Working Reference is a purified antigen or nonadjuvanted harvest material. Qualifying serials shall be produced in accordance with the filed Outline of Production, tested for immunogenicity in accordance with methods deemed appropriate by the Animal and Plant Health Inspection Service, and have a geometric mean relative potency, when compared to the Master Reference, of not greater than 1.0 as established by: independent parallel line assays with five or more replicates; or other valid assay methods for determining relative antigen content which demonstrate linearity, specificity, and reproducibility at least equivalent to the parallel line assay and are acceptable to the Animal and Plant Health Inspection Service.

(2) Qualifying serials used to requalify or extend the dating period of a Master Reference shall be determined to be immunogenic in accordance with methods deemed appropriate by the Animal and Plant Health Inspection Service as provided in paragraph (a)(1) of this section, and, in addition, shall be within their permitted dating period and have been prepared in accordance with the production method described in the currently filed Outline of Production.

(r) *Immunogenicity*. The ability of a biological product to elicit an immune response in animals as determined by test methods or procedures acceptable to the Animal and Plant Health Inspection Service.

[38 FR 8426, Apr. 2, 1973, as amended at 40 FR 45419, Oct. 2, 1975; 41 FR 6751, Feb. 13, 1976; 43 FR 3701, Jan. 27, 1978; 56 FR 66782, 66783 Dec. 26, 1991; 62 FR 19037, Apr. 18, 1997]

§ 101.6 Cell cultures.

When used in conjunction with or in reference to cell cultures, which may be referred to as tissue cultures, the following terms shall mean:

(a) *Batches of primary cells*. A pool of original cells derived from normal tissue up to and including the 10th subculture.

(b) *Cell line*. A pool of cells which are 11 or more subcultures from the tissue of origin.

(c) *Subculture*. Each flask to flask transfer or passage regardless of the number of cell replications.

(d) *Master Cell Stock (MCS)*. The supply of cells of a specific passage level from which cells for production of biologics originate.

[38 FR 8426, Apr. 2, 1973, as amended at 40 FR 45419, Oct. 2, 1975; 49 FR 22624, May 31, 1984]

§ 101.7 Seed organisms.

When used in conjunction with or in reference to seed organisms, the following shall mean:

(a) *Master Seed*. An organism at a specific passage level which has been selected and permanently stored by the producer from which all other seed passages are derived within permitted levels.

(b) *Working Seed*. An organism at a passage level between Master Seed and Production Seed.

(c) *Production Seed*. An organism at a specified passage level which is used without further propagation for initiating preparation of a fraction.

[49 FR 22625, May 31, 1984]

PART 102—LICENSES FOR BIOLOGICAL PRODUCTS

Sec.

102.1 Licenses issued by the Administrator.
102.2 Licenses required.
102.3 License applications.
102.4 U.S. Veterinary Biologics Establishment License.
102.5 U.S. Veterinary Biological Product License.
102.6 Conditional licenses.

AUTHORITY: 21 U.S.C. 151–159; 7 CFR 2.22, 2.80, and 371.4.

§ 102.1 Licenses issued by the Administrator.

Each establishment qualified to prepare biological products under the Virus-Serum-Toxin Act shall hold an unexpired and unrevoked U.S. Veterinary Biologics Establishment License issued by the Administrator and a U.S. Veterinary Biological Product License for each product prepared in such establishment unless the product is subject to the provisions of 9 CFR parts 103 or 106 of this subchapter.

[60 FR 48021, Sept. 18, 1995]

§ 102.2 Licenses required.

(a) Every person who prepares biological products subject to the Virus-Serum-Toxin Act shall hold an unexpired, unsuspended, and unrevoked U.S. Veterinary Biologics Establishment License and at least one unexpired, unsuspended, and unrevoked U.S. Veterinary Biological Product License issued by the Administrator to prepare a biological product.

(b) An applicant who applies for an establishment license must also apply for at least one product license. An establishment license will not be issued without a license authorizing the production of a biological product in the establishment.

[52 FR 11026, Apr. 7, 1987, as amended at 56 FR 66783, Dec. 26, 1991; 61 FR 52873, Oct. 9, 1996]

§ 102.3 License applications.

(a) *U.S. Veterinary Biologics Establishment License.* (1) The operator of each establishment of the kind specified in § 102.2 shall make written application to the Administrator for a license. Blank forms of application will be furnished upon request to Animal and Plant Health Inspection Service.

(2) When a person conducts more than one establishment, a separate application shall be made for each establishment.

(3) Whenever subsidiaries are to operate in an establishment for which license application is made, the applicant shall apply for permission for such subsidiaries to operate in the establishment and furnish therewith a complete statement regarding the relationship between the applicant and the subsidiaries.

(4) Facilities documents, prepared as prescribed in part 108 of this subchapter, shall accompany the application for license unless previously filed with Animal and Plant Health Inspection Service.

(5) Each application for a U.S. Veterinary Biologics Establishment License shall be accompanied by an application for one or more U.S. Veterinary Biological Product Licenses and the supporting documents required by paragraph (b)(2) of this section.

(6) A new application shall be made when a change of ownership, operation, or location of an establishment occurs; or prior to the expiration of a U.S. Veterinary Biologics Establishment License issued for an interim period of time.

(b) *U.S. Veterinary Biological Product License.* (1) The licensee of each establishment or applicant for an establishment license shall make written application to the Administrator for a U.S. Veterinary Biological Product License for each biological product to be prepared in the licensed establishment.

(2) Each application for a U.S. Veterinary Biological Product License shall be supported by:

(i) At least two copies of an Outline of Production prepared in accordance with §§ 114.8 and 114.9 of this subchapter; and

(ii) At least three copies of test reports and research data sufficient to establish purity, safety, potency, and efficacy of the product; and

(iii) Legends prepared as prescribed in § 108.5 of this subchapter designating which facilities are to be used in the preparation of each fraction; and

(iv) Labels in finished form or sketches prepared as prescribed in § 112.5 of this subchapter, together with information regarding all claims to be made on labels and in advertising matter to be used in connection with or related to the biological product.

(Approved by the Office of Management and Budget under control number 0579–0013)

[39 FR 37763, Oct. 24, 1974, as amended at 48 FR 57472, Dec. 30, 1983; 49 FR 21043, May 18, 1984; 50 FR 50763, Dec. 12, 1985; 56 FR 66783, Dec. 26, 1991; 75 FR 20772, Apr. 21, 2010]

§ 102.4 U.S. Veterinary Biologics Establishment License.

(a) Before a U.S. Veterinary Biologics Establishment License will be issued by the Administrator for any establishment, an inspection shall be made to determine whether the condition, equipment, facilities, and the like, of the establishment, and the methods used to prepare biological products are in conformity with the requirements in the regulations.

(b) A license shall not be issued unless:

(1) In the opinion of the Administrator, the condition of the establishment, including its facilities, and the methods of preparation of biological products are such as reasonably to assure that the products shall accomplish the purpose for which they are intended; and

(2) The Administrator is satisfied on the basis of information before him that:

(i) The establishment shall be operated in compliance with the Act and applicable regulations and be under the supervision of person(s) competent in the preparation of biological products; and

(ii) The applicant, or the person having the responsibility for producing biological products in the establishment, or both, is qualified by education and experience, and has demonstrated fitness to produce such products in compliance with the Act and regulations issued pursuant thereto; *Provided*, That, previous violations of the Act, or such regulations or both shall be relevant to the Administrator's determination of fitness.

(3) Written assurance is filed with Animal and Plant Health Inspection Service that the biological products which are licensed to be prepared therein shall not be so advertised as to mislead or deceive the purchasers and that the packages or containers in which the same are to be marketed shall not bear any statement, design, or device which is false or misleading in any particular.

(c) U.S. Veterinary Biologics Establishment Licenses shall be numbered.

(d) Two or more licenses may bear the same number when they are issued for establishments under the same ownership or control, provided a serial letter is added to one or more to identify each license and the product produced thereunder.

(e) When a U.S. Veterinary Biologics Establishment License is issued for an establishment, it shall not apply to more than one person at the same location, except that subsidiaries of the licensee, when named in the license, may operate thereunder at the establishment named. The licensee with its subsidiaries will be held responsible for all operations conducted in the licensed establishment.

(f) When a licensee no longer holds at least one unexpired, unsuspended, or unrevoked product license authorizing the preparation of a biological product, or is in the process of obtaining a product license, the establishment license shall no longer be valid and shall be returned to the Administrator. In the case where an establishment license expires or is suspended or revoked, any product license authorizing preparation of a product at such establishment shall be invalid indefinitely or for as long as the suspension is in effect.

(g) Any license issued under this part to establishments in which biological products are prepared shall be issued on condition that the licensee permit the inspection of such establishments, products, product preparation, and all relevant records as provided in part 115 of this subchapter. Failure to permit inspection may result in the license being suspended or revoked.

(h) The provisions of paragraph (b) of this section shall also be applicable to, and be considered by, the Administrator in connection with each application for an additional product license.

(Approved by the Office of Management and Budget under control number 0579–0013)

[39 FR 37762, Oct. 24, 1974; 39 FR 38364, Nov. 1, 1974, as amended at 41 FR 44359, Oct. 8, 1976; 48 FR 57472, Dec. 30, 1983; 52 FR 11026, Apr. 7, 1987; 52 FR 30131, Aug. 13, 1987; 56 FR 66783, Dec. 26, 1991; 60 FR 48021, Sept. 18, 1995; 61 FR 52873, Oct. 9, 1996; 62 FR 13294, Mar. 20, 1997]

§ 102.5 U.S. Veterinary Biological Product License.

(a) Authorization to produce each biological product shall be specified on a U.S. Veterinary Biological Product License, issued by the Administrator, and supplementary to the U.S. Veterinary Biologics Establishment License named therein.

(b) The following shall appear on the U.S. Veterinary Biological Product License:

(1) The U.S. Veterinary Biologics Establishment License Number for the establishment from which the product is released for marketing.

(2) The true name of the product.

(3) The product code number for the product.

(4) The date of issuance.

(5) Any restrictions designated by the Administrator under paragraph (e) of this section.

(6) When necessary to comply with §102.6 of this part, a termination date and a brief description of requirements to be met for reissuance.

(c) The following provisions shall apply to all licensed biological products:

(1) Licensed biological products shall be prepared as required by the regulations and in accordance with a filed Outline of Production as prescribed in §§114.8 and 114.9 of this subchapter. No change shall be made in the preparation of a biological product without prior approval of the Administrator.

(2) In addition to restrictions imposed by the Administrator pursuant to paragraph (e) of this section, biological products may be subject to restrictions which are imposed by any State or other jurisdiction pertaining to the distribution and use of such products, based on local disease conditions.

(3) When requested by the Administrator, a licensee shall submit a list of licensed biological products prepared in the licensed establishment.

(d) Where the Administrator determines that the protection of domestic animals or the public health, interest, or safety, or both, necessitates restrictions on the use of a product, the product shall be subject to such additional restrictions as are prescribed on the license. Such restrictions may include, but are not limited to, limits on distribution of the product or provisions that the biological product is restricted to use by veterinarians, or under the supervision of veterinarians, or both.

(e) Any person may request that the distribution and use of a veterinary biological product be restricted if the restriction pertains to the protection of domestic animals or the public health, interest, or safety, or both. All requests must be sent, in writing, to the Director, Center for Veterinary Biologics, Policy, Evaluation, and Licensing, 1920 Dayton Avenue, P.O. Box 844, Ames, IA 50010. Requests must specify the restriction(s) being requested and must explain why the restrictions are needed. Copies of any supporting documents, such as scientific literature, published or unpublished articles, or data from tests, should be attached to the request. When a decision is reached regarding the request, the person submitting the request will be sent written notification of such decision.

(Approved by the Office of Management and Budget under control number 0579–0013)

[39 FR 37763, Oct. 24, 1974, as amended at 48 FR 57472, Dec. 30, 1983; 50 FR 50764, Dec. 12, 1985; 52 FR 11026, Apr. 7, 1987; 56 FR 66783, Dec. 26, 1991; 57 FR 38760, Aug. 27, 1992; 59 FR 67616, Dec. 30, 1994; 62 FR 13294, Mar. 20, 1997; 64 FR 43044, Aug. 9, 1999; 75 FR 20772, Apr. 21, 2010]

§102.6 Conditional licenses.

In order to meet an emergency condition, limited market, local situation, or other special circumstance, including production solely for intrastate use under a State-operated program, the Administrator may, in response to an application submitted as specified in §102.3(b) of this part, issue a conditional U.S. Veterinary Biological Product License to an establishment under an expedited procedure which assures purity and safety, and a reasonable expectation of efficacy. Preparation of products under a conditional license shall be in compliance with all applicable regulations and standards and may be restricted as follows:

(a) The preparation may be limited to a predetermined time period which shall be established at the time of issuance and specified on the license. Prior to termination of the license, the licensee may request reissuance. Such requests shall be substantiated with data and information obtained since the license was issued. After considering all data and information available, the Administrator shall either reissue the U.S. Veterinary Biological Product License or allow it to terminate.

(b) Distribution may be limited to the extent necessary to assure that the product will meet the basic criteria for issuance of the conditional license.

(c) Labeling for the product may be required to contain information on the conditional status of the license.

[52 FR 11026, Apr. 7, 1987, as amended at 60 FR 48021; Sept. 18, 1995]